

REMARKS

Reconsideration of the rejection of all claims is respectfully requested in view of the above amendments and the following remarks.

Claim Status

The previous allowance of claim 13 apparently has been withdrawn without comment, inasmuch as claim 13 is now rejected. Moreover, the previous indication of allowability of claim 10 apparently has been withdrawn inasmuch as claim 10 is now rejected. However, claims 11 and 12 remain objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form. Claims 1-4 and 15 were previously cancelled, and claims 5-10, 13, 14 and 16-19 are now rejected.

Claim Amendments

Claims 9 and 18 have been combined to form new independent claim 20, wherein the R² definition from claim 9 is incorporated and ring C is defined as pyrazolyl. Claims 7, 9 and 18 have thereby become redundant and have been newly cancelled. Additionally, method of treatment claims 13 and 17 have been cancelled. Process for making claim 19 has been amended to be consistent with the reduced compound scope of claim 20, upon which it is now dependent. The dependency of the remaining claims has been adjusted accordingly where necessary. These amendments are being made with the hope of expediting the prosecution of this application, and are made without abandonment or prejudice to Applicants' right to prosecute any subject matter thereby deleted in one or more continuing applications.

It should be clear that no new matter has been added by the above amendments, and entry thereof is believed to be in order and is respectfully requested. Following entry of the above amendments, independent claim 20 and dependent claims 5, 6, 8, 10-12, 14, 16 and 19 are pending in this application.

Claim Rejections - 35 USC § 112, Second Paragraph

Claims 13 and 17 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The Examiner asserts that the recitation in these claims of "a method for producing an antiangiogenic and/or vascular permeability reducing effect..." makes them indefinite because, "Defining a disease(s) by its (their) underlying cause renders the scope of intended uses indeterminate since the claim language may read on diseases not yet known to be caused by or affected by such action or in ways not yet understood." While Applicants disagree with this ground for rejection as not being founded in any statute, regulation, case law, or even the MPEP, claims 13 and 17 have been cancelled above, without prejudice, solely for the purpose of expediting the allowance of this application.

Claim Rejections - 35 USC § 112, First Paragraph

Claims 5-10, 13, 14 and 16-19 are rejected under 35 U.S.C. 112, first paragraph, because the specification

... while being enabling for the making and using of compounds of formula II wherein:

- a. ring C is *pyrazolyl*, and
- b. R^2 (at the 7-position) represents *methoxyethoxy*-, *3-morpholinopropoxy*-, *3-(4-methylpiperazin-1-yl)propoxy*-, *1-methylpiperidin-4-ylmethoxy*-, *(2-methoxyethoxy)ethoxy*-, *2-(imidazol-1-yl)ethoxy*-, *2-(1,2,3-triazol-1-yl)ethoxy*-,

does not reasonably provide enablement for the making and using of compounds of formula II wherein ring C is another 5- or 6-membered heterocyclic moiety, and R^2 represents other groups selected from the list of R^5X^1 -. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

(Action at page 3; emphasis in original).

This ground for rejection is respectfully traversed, but in any event it is believed that this ground for rejection has been overcome by the above amendments.

First of all, by reciting specific groups for Ring C and R² it appears that the Examiner may be trying to indicate the scope of direct exemplification of ring C and R². If that is the case, Applicants wish to point out that the R² groups that have been *expressly* exemplified are as follows:

methoxy,
2-methoxyethoxy,
3-morpholinopropoxy,
2-(imidazol-1-yl)ethoxy,
2-(2-methoxyethoxy)ethoxy,
3-methylsulphonylpropoxy,
3-(4-methylpiperazin-1-yl)propoxy,
1-methylpiperidin-4-ylmethoxy,
2-(1,2,3-triazol-1-yl)ethoxy, and
1-(2-methylsulphonylethyl)piperidin-4-ylmethoxy,

wherein the underlined groups were not listed by the Examiner.

Nevertheless, there is no requirement in the law or regulations that every compound coming within the scope of chemical claims such as these be exemplified in the specification. The specification is directed to persons skilled in the art, and the skilled chemist in this art is quite capable of synthesizing compounds of interest within the scope of these claims (and the starting materials therefore) without need for each and every compound and its process for manufacture being set forth in the specification. The Examiner is well aware from the thousands of chemical patents issued by this Group and Art Unit over at least the past decade that exemplification of each and every compound within a generic claim, or each moiety within a Markush grouping, has never been a requirement, except perhaps in cases involving truly exotic chemistry or starting materials, which clearly is not the case here. However, if this is the Examiner's intent, the undersigned is not aware of any recent change in the law, case law, regulations or even the MPEP that would support this dramatic shift from the well established precedent of the past, and would appreciate being informed of the support on which this shift in position is based so that it can be considered and appropriately addressed in the next response or on appeal.

In the absence of any support for such a drastic change in position, it has been assumed that the Examiner is now objecting to the breadth of compounds encompassed by

combination of the generic definitions of ring C and group R² as not being sufficiently represented by the compounds that have been specifically named and exemplified. While Applicants do not agree with this position, in an effort to expedite the prosecution of this application to allowance, the above amendments (via new independent claim 20) limit the scope of ring C to recite *only pyrazolyl*, and limit the scope of R² by incorporation of the significantly narrower definitions from now-cancelled claim 9. It is respectfully submitted that the exemplified compounds are clearly representative of compounds wherein ring C is pyrazolyl and of compounds wherein R² is as now defined, and no more is required.

With respect to the Examiner's assertions under the *Ex parte Forman* and *In re Wands* factors, Applicants wish to note as follows:

- **The breadth of the claims:** The Examiner focuses particularly on the breadth of the definitions of ring C and group R². As noted above, in new independent claim 20 ring C has been limited to pyrazolyl, and the definition of group R² at the 7-position of the quinazoline ring has been significantly narrowed.
- **The amount of direction or guidance presented:** In view of the significant reduction of scope of the claims with respect to ring C and group R² (on which this rejection is focused), it is respectfully submitted that the examples are more than adequately representative of pyrazolyl as ring C and of the types of groups encompassed within the significantly reduced scope of R². Again it is noted that there never has been, and is not now, any legal requirement that each and every compound or group within the scope of chemical compound claims be exemplified, provided that the skill and knowledge in the art with the guidance provided by the specification is sufficient to enable the skilled person to make and use the invention. It is respectfully submitted that the exemplified compounds and groups therein are sufficiently representative of the narrowed scope of the present claims such that the skilled person is so enabled. The Examiner is also reminded of the declaration of Stephen Robert Wedge that was submitted with the Amendment and Response filed November 19, 2004, which included biological data for exemplified compounds.

- **State of the prior art and relative skill of those in the art:** The Examiner is clearly aware that the quinazoline art at the time of this invention extended far beyond the Myers '969 disclosure, as is also clear from the Information Disclosure Statements and forms PTO-1449 filed in this application. Persons skilled in this art were accustomed to working with a wide variety of chemical groups and were quite capable of using that skill and experience to assemble those groups to make the compounds taught by this application and presently claimed. Such persons were also accustomed to routinely testing such compounds in a variety of assays well known from the patent and published literature, in addition to the assays set out in the present specification, to determine the relative activity of such compounds. In addition to the reduced scope of the compound claims presently pending, the Examiner is reminded that the method claims have now been cancelled. Again, the Examiner's attention is called to the biological data provided with the Wedge Declaration.
- **The predictability or unpredictability of the art & the quantity of experimentation necessary:** It is believed that the particular assertions of inadequacy made under this heading have been obviated by the reduction in scope of the compound claims relative to the representative examples and the biological data previously provided with the Wedge Declaration, as well as the cancellation of claims 13 and 17.

Therefore, in view of the claim amendments and the other factors noted above, it is believed that any ground for this rejection has been obviated or overcome, and withdrawal of this ground for rejection is respectfully requested.

Claim Rejections - 35 USC § 103- Myers '969

Applicants note with appreciation that the Examiner has now recognized her misunderstanding with respect to the term "thiophenoxy," and thus has withdrawn the previously stated rejection over Myers '969 *in view of Hawley's*. However, it was thought that clearing up this misunderstanding would finally *reinstate the previous allowance* of compound claim 18 and the compound claims dependent thereon. The Examiner will recall

that these compound claims *were specifically allowed* over the same Myers *et al.* disclosure that is now again cited in the present rejection,¹ before prosecution of this application was side-tracked, first by the Examiner's erroneous "new matter" rejection and then by the "thiophenoxy" misconception. Since these "new matter" and "thiophenoxy" grounds for rejection have now been withdrawn, it is thought that perhaps the Examiner has forgotten that these compound claims had already been allowed over the same Myers *et al.* disclosure.

Very briefly, in the first Action dated May 6, 2002, the Examiner asserted that Myers *et al.* WO 95/15758 "inherently anticipated" original claims 1 and 17² on grounds that the compound, 4-(3-aminopyrazolyl)-6,7-dimethoxyquinazoline hydrochloride named in Myers *et al.* was embraced by the original claims. In the Amendment and Response filed November 6, 2002, narrower compound claim 4 was rewritten in independent form as new compound claim 18, to further distinguish from the Meyer *et al.* disclosure. As a result of the amendments, compound claims 2, 3, 5-12, 14 and 17-19 were allowed in the Action dated January 29, 2003, the Examiner stating:

Claims 2, 3, 5-12, 14 and 17-19 are allowed. The teaching of Myers *et al.* does not disclose species having a substituent on the quinazoline ring *in combination with* a heterocycle attached to a group equivalent to the instant variable Z.

(Action January 29, 2003 at page 3; emphasis added). Specifically the Examiner recognized that the allowed claims (then and now) have a substituent Zb, which can be *only -O- or -S-*, linking a *heterocyclic ring* (now specifically a *pyrazolyl ring*) to the 4-position of the quinazoline ring.

In their next response of July 29, 2003, Applicants amended the method claims, which had remained rejected, but did not amend compound claim 18. Nevertheless, in the next Action dated October 22, 2003, the Examiner rejected claim 18 (and claims dependent

¹ As summarized below, the initial obviousness rejection that was previously overcome (resulting in the allowance of compound claims 18 *et seq.*) was based on Myers *et al.* WO 95/15758, the substantive disclosure of which is identical to the Myers '969 reference now applied by the Examiner. Specifically, Myers '969 granted on a continuation of application No. PCT/US94/14180, which PCT application published as WO 95/15758.

² The remaining claims were not then treated on the merits since they were in an improper multiple dependent form.

thereon) for adding new matter, even though no further amendment had been made to claim 18. The Examiner's error with respect to the new matter rejection was straightened out as a result of Applicants next response dated April 22, 2004, and the allowance of compound claims 18 et seq. *should have been reinstated*.

However, in the next Action dated of May 19, 2004, previously-allowed claims 5-12, 14, and 17-19 were *now* rejected under Myers '969 (disclosure substantively identical to Myers et al. WO 95/15758 as noted above) based on a misunderstanding of the term "thiophenoxy." The Examiner thus began a series of three Actions wherein the previously allowed compound claims were rejected on grounds that are now acknowledged as having been based on a misinterpretation of the term "thiophenoxy."

Again, Applicants very much appreciate that the obviousness rejection based on the "thiophenoxy" misconception has been withdrawn, but are disappointed that the Examiner has *now* rejected the compound claims based on the same Myers et al. disclosure that was previously raised and overcome, resulting in the allowance of the compound claims in the January 29, 2003 Action. The stated reason for that allowance of compound claim 18 et seq. is equally, if not even more, compelling for the allowance of narrower independent compound claim 20 now pending in this application.

In the present Action the obviousness rejection over Myers '969 is stated by the Examiner as follows:

3. Claims 5-9, 14, 16-19 remain rejected under 35 U.S.C. 103(a) as being unpatentable over **Myers et. al.** (US 6,645,969 B1).

While applicant is correct on the meaning of the term "thiophenoxy", the equivalent teaching in US'969 cannot be ignored. Besides the two quinazoline compounds having "thiophenoxy" mentioned in the previous action, Myers et. al. also list other quinazoline compounds with a heterocyclic ring corresponding to the instant ring C, namely:

4-(thien-3-yl)-6,7-dimethoxyquinazoline;

4-(pyrazol-3-ylamino)-6,7-dimethoxyquinazoline hydrochloride.

While the above species do not anticipate the instant scope in view of the proviso for R² in claim 18, they are obvious variants since Myers et. al. teach other substituents at the 7-position on the quinazoline ring as well - see definition of R₇ which includes alkylthio, hydroxyl, cycloalkyl, etc.

Myers et. al. also teach different linking groups represented by X which includes a bond, -O-, -S-, -NH, etc., and various aryl as well as heteroaryl ring

represented by Ar. Also, see species in columns 14-16, which collectively teach various aspects of applicant's invention.

With the equivalency teaching provided in the definition of variables X, Ar of the disclosed formula I on column 3 of US'969, it is clear that -O-, or -S- can replace the amino group at the 4-position (see the definition of X on line 21). Also, heterocyclic moieties such as: *thienyl*, or *pyrazolyl* can replace the phenyl group in "thiophenoxy" (phenyl-S-). Likewise, there is also equivalency teaching for substituents at the 6- and 7-position (corresponding to the instant variable R² or R^{2a}), in which *alkylthio*, *hydroxyl*, *carboxy*, *carbalkoxy* can replace the alkoxy group (see definitions of R₇ on column 3, line 36).

Thus, it would have been obvious to make compounds of formula II wherein R² is other than alkoxy and C is thienyl, pyrazolyl, etc. having O/S links in view of the express equivalency teachings outlined above.

(Present Action at pages 8-9).

The 4-(pyrazol-3-ylamino)-6,7-dimethoxyquinazoline hydrochloride compound of Myers et al. now cited by the Examiner is the same compound (same mp, same position in the "representative list of compounds,"³ updated nomenclature) as the 4-(3-aminopyrazolyl)-6,7-dimethoxyquinazoline hydrochloride that was cited in the May 6, 2002 Action, over which compound claims 18 et seq. were allowed in the January 29, 2003 Action. However, the allowed claims (and present claim 20) have a substituent Zb, which can be only -O- or -S-, linking a heterocyclic ring (now specifically a pyrazolyl ring) to the 4-position of the quinazoline ring. On the other hand, the majority of the named compounds in Myers '969 have a *phenyl ring* at the 4-position of the quinazoline ring, but the named compounds of Myers '969 *having a 5- or 6-membered heterocyclic ring are not linked via -O- or -S- which are the only values for Zb in then-pending claim 18, as well as claim 20 of the present application*. In Myers '969, when ring Ar is a 5- or 6-membered heterocyclic ring, it is linked directly to the quinazoline ring or it is linked via a nitrogen atom. Accordingly it is respectfully submitted that there is no suggestion in Myers to make the to make the substitutions or combinations needed to arrive at the presently claimed compounds in the manner asserted by the Examiner. In fact Myers '969 teaches away from the 4-position

³ This compound appears at page 15, lines 22-23 of Myers et al. WO 95/15758 and at column 9, lines 61-62 of Myers '969.

substituent being a 5-6 membered heterocyclic ring in that it states that ring Ar is preferably phenyl or naphthyl (column 4 line 44), preferably phenyl (column 4 line 51). Moreover, Myers '969 have a very limited number of substituents at the 6 and 7-positions of the quinazoline ring, being either 6,7-dihydrogen, 6-chloro and 7-hydrogen, 6,7-dimethoxy or 6,7-dimethyl, and that of these combinations of 6- and 7-position substituents falls within the scope of new compound claim 20 or of now cancelled compound claim 18. Therefore structurally, the compounds of then pending claim 18 (and narrower present claim 20) are not suggested by the compounds named in Myers '969.

As Applicants have previously pointed out, there is a very small area of overlap between claim 18 (now of reduced scope as present claim 20) and Myers '969. Focusing on the 7-position substituent in particular, the values for R_7 in Myers '969 can be divided up into groups:

Group 1: hydrogen, alkyl, alkoxy, haloalkyl, aralkoxy;

Group 2: cycloalkyl, halo, carboxy, carbalkoxy (or alkoxycarbonyl);

Group 3: alkylthio, hydroxy, aryl.

- The group 1 values are excluded as values for R^2 in the present claims by means of the proviso in claim 20. With regard to aralkoxy, the only aralkoxy value possible in the definition of R^2 is phenoxy, *i.e.*, when R^5 is selected from group 8), R^{29} is phenyl and X^1 is -O- and R^2 cannot be phenoxy per the proviso in claim 20.
- The group 2 values are not values of R^2 .
- The group 3 values represent the minor area of generic overlap and the only aryl value in the overlap is phenyl, *i.e.*, when R^5 is selected from group 8) and R^{29} is phenyl.

Therefore very minor overlap within the broad genus occurs only when the 7-position substituent R^2 is phenyl, hydroxy or C_{1-4} alkylthio (*i.e.*, R^2 is R^5X^1 wherein X^1 is -S- and R^5 is selected from group 1) and is C_{1-4} alkyl).

It is respectfully submitted that there is no suggestion or motivation in Myers '969 as a whole that would lead one to combine the necessary parts of the generic teaching so as to make compounds in this minor area of overlap. In fact, the preferences and exemplification in Myers '969 would lead one

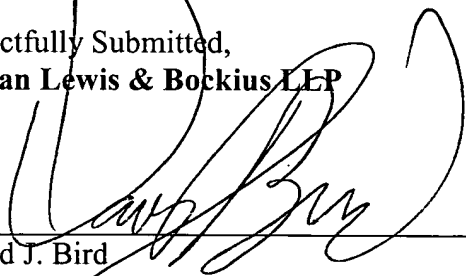
away from this minor area of overlap. Therefore, the present claims are structurally distinct from the teachings of Myers '969 as a whole, and Myers '969 does not give rise to *prima facie* obviousness.

Conclusion

For the reasons detailed above, Applicants continue to maintain that the presently claimed compounds are structurally distinct from the teachings of Myers '969. Accordingly, all claims are believed to be in condition for allowance, and a Notice to that effect is respectfully requested.

EXCEPT for issue fees payable under 37 C.F.R. § 1.18, the Director is hereby authorized by this paper to charge any additional fees during the entire pendency of this application including fees due under 37 C.F.R. §§ 1.16 and 1.17 which may be required, including any required extension of time fees, or credit any overpayment to Deposit Account 50-0310. This paragraph is intended to be a CONSTRUCTIVE PETITION FOR EXTENSION OF TIME in accordance with 37 C.F.R. § 1.136(a)(3).

Respectfully Submitted,
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